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(54) Nucleosides of 5-monofluoromethyluracil and 5-difluoromethyluracil.

(57) A method for synthesizing monofluoromethyl- and difluoromethyluracil nucleosides from the corresponding thymine nucleosides is developed. These compounds which contain a partially fluorinated methyl group at the C-5 position (a new class of nucleosides) are potential antiviral and/or anti-cancer agents. The major features of the preparative route involve bromination of suitably protected thymine nucleosides followed by fluoride treatment.

EP 0 222 192 A2

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5  
10 Nucleosides of 5-Monofluoromethyluracil and  
5-Difluoromethyluracil

The invention described herein was made in the course of  
work under a grant from the U.S. Department of Health and  
15 Human Services.

BACKGROUND

20 5-Trifluoromethyluracil was originally synthesized in  
very low yield by a multistep procedure starting from  
trifluoroacetone-cyanohydrin (Heidelberger, et al., J.  
Am. Chem. Soc., 84, 3527 (1962); J. Med. Chem. 7, 1  
(1964)). Later, this compound was prepared more con-  
25 veniently from uracil-5-carboxylic acid by treatment  
with sulfur tetrafluoride (Mertes, et al., J. Med.  
Chem., 9, 876 (1964)). The 2'-deoxynucleoside, i.e., 1-  
(2'-deoxy- $\beta$ -D-erythropentofuranosyl)-5-trifluoromethyl-  
uracil or F<sub>3</sub>TDR, was prepared by condensation of the  
30 base and sugar halide in very low yield. (Heidelberger,  
Progr. Nucleic Acid Res. Mol. Biol., 4, 1 (1965); Cancer  
Res., 30, 1549 (1970)).

5-Difluoromethyluracil was also prepared but was found  
35 to be extremely labile in neutral aqueous media (Mertes,  
et al., loc. cit). No nucleoside containing this base has  
been synthesized. Attempts to synthesize 5-monofluoro-

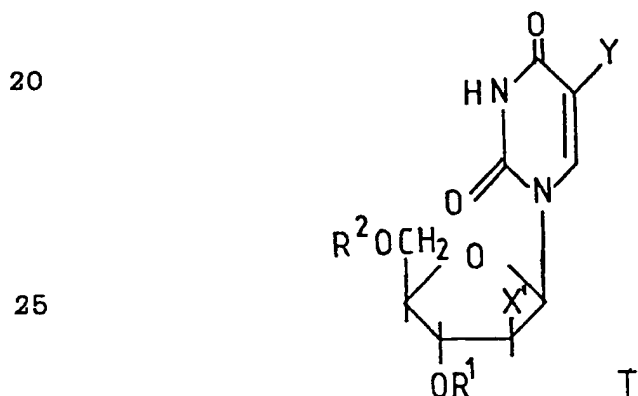
1 uracil have failed (Mertes, loc. cit). No 5-monofluoro-  
methyluracil nucleoside is known.

Our theoretical considerations suggest that substitution  
5 of the N-1 position of 5-(partially-fluorinated)-methyl-  
uracils with an alkyl or sugar moiety should decrease  
the lability of the fluorine in the heterocyclic base.  
Therefore, nucleosides containing 5-(partially fluori-  
nated) methyluracils should be obtainable by synthesis  
10 from a preformed nucleoside.

#### SUMMARY

15 Nucleosides of the invention can be represented by  
Formula I as follows:

Formula I



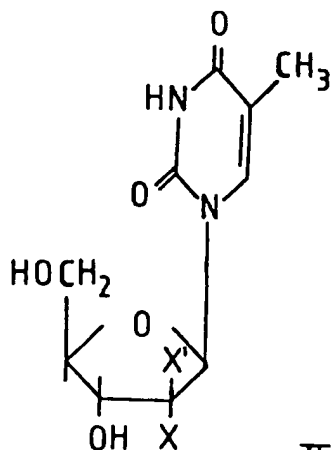
30 Wherein either X or X' is always H.  
X or X' is H, OR<sup>3</sup>, or a halogen such as fluorine,  
chlorine, bromine or iodine as well as pseudohalogen  
such as lower alkylsulfonyl group of 1 to 5 carbons such  
as methyl-, ethyl- propyl-, isopropyl-, butyl-, isobu-  
35 tyl-, sec-butyl-, tert-butyl, and pentylsulfonyl or  
arylsulfonyl such als benzene-, p-toluene-, p-nitro-  
benzenesulfonyl grouping.

- 1 Y is monofluoromethyl ( $\text{CH}_2\text{F}$ ) or difluoromethyl ( $\text{CHF}_2$ ).  
 $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are the same or different and are hydrogen  
 or aryl groups of 1 to 20 carbon atoms such as formyl,  
 acetyl, propionyl, isopropionyl, butyryl, isobutyryl,  
 5 tert-butyl, valeryl, pivaloyl, caproyl, capryl, lauryl,  
 myristyl, palmityl, stearyl, arachidyl, stilligyl,  
 palmitoyl, oleyl, linolenyl, arachidonyl and the like, or  
 trisubstituted silyl groups such as tert-butyl-dimethyl-  
 silyl, tert-butyldiphenylsilyl, dimethylphenylsilyl and  
 10 the like.

## DESCRIPTION OF INVENTION

- 15 The present invention relates to the novel class of  
 nucleosides which contain 5-monofluoromethyluracil or 5-  
 difluoromethyluracil as their aglycon. A further aspect  
 of the present invention relates to processes for prepa-  
 ring uracil nucleosides containing a partially fluori-  
 20 nated methyl group at the C-5 position and intermediates  
 useful therein.

The starting materials for the process of the present  
 invention can be subsumed under general Formula II, as  
 25 follows:



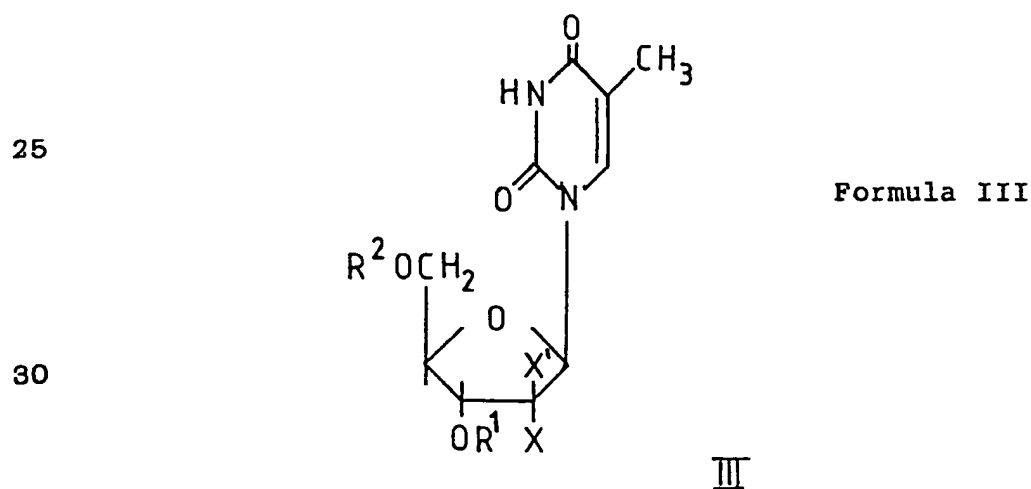
Formula II

II

35 X or  $\text{X}^1$  is hydrogen  
 X or  $\text{X}^1$  is as defined previously.

1 Nucleosides of Formula II are acylated with alkanolic  
 acid chloride or alkanolic acid chloride or alkanolic acid  
 anhydride in organic base such as pyridine or triethyla-  
 mine. Acylation of Formula II nucleosides is also achie-  
 5 ved with alkanolic acid chloride or alkanolic acid an-  
 hydride in aprotic solvent such as methylene chloride,  
 chloroform, dichloroethane or tetrachloroethane in the  
 presence of organic base such as pyridine, lutidine,  
 collidine, triethylamine, N,N-diethylaniline, p-(di-  
 10 menthylamine)pyridine, 1,8-diazabicyclo(5,4,0)undec-7-  
 4ene or 1,5-diazabicyclo(4,3,0)-non-5-ene.

Upon completion of the reaction, the reaction mixture is  
 quenched suitably, by adding excess alkanol such as  
 15 methanol, ethanol, propanol and the like, to hydrolyze  
 the acylating reagent. After concentration of the mix-  
 ture, the acylated intermediates can be obtained in pure  
 condition either by direct crystallization of the resi-  
 due from various solvents or solvent systems, or by  
 20 chromatography over a column of silica gel G60 using  
 various solvent systems. The acylated intermediates



obtained by the above procedure can be presented under  
 35 general Formula III, wherein  
 X or X<sub>1</sub> is always hydrogen  
 X or X<sub>1</sub> is OR<sub>3</sub>, or a halogen such as fluorine, chlorine,

- 1 bromine or iodine as well as pseudohalogen such as low  $r$   
alkylsulfonyl group of 1 to 5 carbons such as methyl-,  
ethyl-, propyl-, isopropyl, butyl-, isobutyl-, sec-  
butyl, tert-butyl- and pentylsulfonyl or arylsulfonyl  
5 such as benzene-, p-toluene-, p-nitrobenzenesulfonyl  
grouping.
- 1  $R^1$ , 2  $R^2$  and 3  $R^3$  are the same and are aryl groups of 1 to  
20 carbon atoms such as formyl, acetyl, propionyl, iso-  
10 propionyl, butyryl, isobutyryl, tert-butyryl, valeryl,  
pivaloyl, caproyl, capryl, lauryl, myristyl, palmityl,  
stearyl, arachidyl, stearic, palmitoyl, oleyl,  
linolenyl, arachidonyl and the like.
- 15 Nucleosides of Formula II are also converted into the  
corresponding partially silylated intermediates by  
treatment with trisubstituted-silyl chloride such as  
tert-butyldimethylsilyl, tert-butyldiphenylsilyl or  
dimethylphenylsilyl chloride in organic base such as  
20 pyridine or triethylamine. Silylation of Formula II  
nucleosides can also be performed with trisubstituted-  
silyl chloride in aprotic solvent such as methylene  
chloride, chloroform, dichloroethane, tetrahydrofuran,  
dioxan, benzene, acetonitrile, ethyl acetate and the  
25 like in the presence of organic base such as pyridine,  
lutidine, collidine, triethylamine. N,N-diethylaniline,  
p-(dimethylamino)pyridine, 1,8-diazabicyclo(5,4,0)undec-  
7-ene or 1,5-diazabicyclo(4,3,0)non-5-ene. The silyla-  
tion reaction is carried out at  $-40^{\circ}$  to  $174^{\circ}$  C (preferably  
30 from  $20^{\circ}$  to  $30^{\circ}$  C), in a period of from 1 hour to 6 days.

When the reaction is carried out without solvent, or in a  
water-miscible aprotic solvent, the mixture is concen-  
trated in vacuo, the residue dissolved in an aprotic  
35 solvent such as methylene chloride, chloroform, benzene  
or the like, and washed with water, dried over sodium  
sulfate or magnesium sulfate and then concentrated in

- 1 vacuo. After the reaction is performed in an aprotic  
solvent not missible with water, the mixture is added  
into cold water, the organic layer separated, dried over  
sodium sulfate or magnesium sulfate, and then concen-  
5 trated in vacuo. The residue is purified either by  
direct crystallization or by chromatograhly on a silica  
gel G60 column using various solvent systems.

- The silhylated intermediates can be subsumed under  
10 general Formula III wherein:  
X or X<sub>1</sub><sup>1</sup> is hydrogen.  
X or X<sub>1</sub><sup>1</sup> is OR<sub>3</sub>, a halogen such as fluorine, chlorine,  
bromine or iodine as well as a pseudohalogen such as the  
lower alkylsulfonyl group of 1 to 5 carbons such as  
15 methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-,  
sec-butyl-, tert-butyl and pentylsulfonyl or arylsul-  
fonyl such als benzene-, p-toluene-, p-nitrobenzenesul-  
fonyl grouping.

- 20 Among R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>, one or two are trisubstituted-silyl  
groups such as tert-butyldimethyl-, tert-butyldiphenyl-  
or phenyldimethylsilyl groupings, and the rest are  
hydrogen.

- 25 The intermediates of Formula III nucleosides are reacted  
with 1 or 2 equivalents of bromine under ultraviolet  
light irradiation in polyhalogenated carbon solvent such  
as carbon tetrachloride at a temperature range of from  
0<sup>0</sup> to 77 C in a period of from 1 to 6 hours. When 1  
30 equivalent of bromine is used, 5-monobromomethyluracil  
nucleosides (Formula I, Y = CH<sub>2</sub>Br) are formed. Reaction  
of Formula III intermediates with 2 equivalents of bro-  
mine results in the formation of 5-dibromomethyluracil  
nucleosides (Formula I, Y = CHBR<sub>2</sub>).  
35

Upon completion of the reaction, nitrogen gas is bubbled  
through the mixture for a period of from 10 minutes to 1

1 hour (preferably 30 minutes), to remove hydrogen bromide  
which is produced during the bromination reaction. The  
mixture is then concentrated in vacuo to afford crude  
bromomethyluracil intermediates (Formula I, Y = CH<sub>2</sub>Br or  
5 CHBr<sub>2</sub>) which can be purified as a very unstable powder.  
More practically, the mixture can be fluorinated directly  
without purification of the bromomethyl-uracil inter-  
mediates. Thus, the crude intermediates are dissolved in  
an appropriate, aprotic solvent and a fluorinating agent  
10 is added. When silver fluoride is used as a fluorinating  
agent, acetonitrile is the preferred solvent. When  
tetrabutylammonium fluoride is employed as the fluorina-  
ting agent tetra-hydrofuran is the more suitable sol-  
vent. Acetone is recommended when Amberlyst A-26 (F<sup>-</sup>) is  
15 used as the fluorinating agent.

The mixture is stirred vigorously at a temperature  
range of from -40<sup>o</sup> to 80<sup>o</sup> C (preferably from -10<sup>o</sup> to  
30<sup>o</sup> C), for a period of from 5 minutes to 5 hours. The  
20 mixture is filtered from insoluble materials and the  
filtrate is washed with water, dried over sodium sul-  
fate or magnesium sulfate, concentrated in vacuo, and  
the residue chromatographed over a column of silica gel  
G60 using various solvent systems, preferably n-hexane-  
25 ethyl acetate or a methylene chloride-tetrahydrofuran  
combination.

The free Formula I nucleosides wherein Y is CH<sub>2</sub>F or CHF<sub>2</sub>  
and R<sub>1</sub> and R<sub>2</sub> are hydrogen, is prepared from the corres-  
30 ponding acyl intermediates (Formula III, wherein Y is  
CH<sub>2</sub>F or CHF<sub>2</sub>, R<sub>1</sub> and R<sub>2</sub> are the same and alkonyl groups)  
by treatment with mineral acid in water or alkanol,  
preferably 1 % to 5 % hydrogen chloride in methanol.  
More preferably, the free nucleosides of Formula I are  
35 prepared from the corresponding partially silylated  
intermediates (Formula III, Y is CH<sub>2</sub>F or CHF<sub>2</sub>, R<sub>1</sub> and/or  
R<sub>2</sub> is/are trisubstituted silyl and X or X<sub>1</sub> is OH or



- 1 trisubstituted silyloxy group) by treatment with fluoride ion in an appropriate solvent, preferably with tetra-n-butylammonium fluoride in tetrahydrofuran.
- 5 The free nucleosides (Formula I, Y is  $\text{CH}_2\text{F}$  or  $\text{CHF}_2$ ,  $\text{R}^1$  and  $\text{R}^2$  are hydrogen) and their acylated analogs (Formula I, Y is  $\text{CH}_2\text{F}$  or  $\text{CHF}_2$ ,  $\text{R}^1$  and  $\text{R}^2$  are the same or different and alkanoyl) may be useful therapeutic agents exhibiting antiviral and/or anticancer activity, and may
- 10 be employed in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier which can be an organic or inorganic inert carrier material suitable for enteral or parenteral administration such as, for example, water,
- 15 gelatin, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical preparations can be made up in solid form (e.g., as tablets, dragees, suppositories or capsules), or in liquid form (e.g., as
- 20 solutions, suspensions or emulsions). The preparations may be sterilized and/or may contain adjuvants such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure, or buffers. Such preparations may also contain other therapeutic agents.
- 25 The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

30

## EXAMPLE 1

- 1-(2-Deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)thymine (1.5 g, 5.76 mmol) is dissolved in dry pyridine (15 ml) and
- 35 acetic anhydride (5 ml) is added. The mixture is stirred overnight at room temperature and is then concentrated in vacuo. The residue is chromatographed on a column of

1 silica gel G60 using n-hexano-ethyl acetate (1:2) as the  
 eluent. Upon evaporation of the major UV-absorbing frac-  
 tion, 1-(3, 5-di-O-acetyl-2-deoxy-2-fluoro- $\beta$ -D-arabino-  
 furanosyl)thymine (1.62 g, 82 %) is obtained as a  
 5 colorless amorphous solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.94 (3H, s, Me), 2.13 (3H, s, Ac),  
 2.17 (3H, s, Ac), 4.25 (1H, m, H-4'), 4.44 (2H, m, H-  
 5'5"), 5.10 (1H, dd, H-2', J<sub>2',F</sub> = 49.95, J<sub>1',2'</sub> = 2.74  
 10 Hz), 5.23 (1H, dd, H-3', J<sub>2',F</sub> = 16.88, J<sub>2',3'</sub> = 2.61),  
 6.22 (1H, dd, H-1', J<sub>1',F</sub> = 21.95, J<sub>1',2'</sub> = 2.74), 7.33  
 (1H, s, H-6), 9.91 (1H, s, NH, exchangeable).

Microanalysis (C<sub>14</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>7</sub>). Calcd: C, 48.84; H, 4.98; N, 8.14.  
 15 Found: C, 48.98; H, 5.12; N, 8.08.

By following the same procedure but using the correspon-  
 ding 2'-substituted nucleosides as starting materials,  
 the following compounds are also prepared:

- 20 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy- $\beta$ -D-  
 arabinofuranosyl)thymine.  
 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy- $\beta$ -D-  
 arabinofuranosyl)thymine.  
 25 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo- $\beta$ -D-  
 arabinofuranosyl)thymine.  
 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro- $\beta$ -D-  
 ribofuranosyl)thymine.  
 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy- $\beta$ -D-  
 30 ribofuranosyl)thymine.  
 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy- $\beta$ -D-  
 ribofuranosyl)thymine.  
 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo- $\beta$ -D-  
 ribofuranosyl)thymine.

## 1 EXAMPLE 2

A mixture of thymidine (0.50 g, 2.06 mmol) and tert-butylldiphenylsilyl chloride (0.60 ml, 2.31 mmol) in dry  
5 pyridine (10 ml) is stirred overnight at room temperature, and then concentrated in vacuo. The residue is dissolved in methylene chloride and the solution washed with water, dried over sodium sulfate and concentrated  
10 in vacuo. The residue is crystallized from acetone-n-hexane to afford S'-0-tert-butylldiphenylsilylthymidine (600 mg), mp 170-171 °C. An additional amount (150 mg) of the silylated product is obtained from the mother  
liquor, giving a total yield of 76 %. <sup>1</sup>H MNR (CDCl<sub>3</sub>)  
1.09 (9H, s, t-Bu), 1.64 (3H, s, Me), 1.94-2.63 (2H, m,  
15 H-2', 2''), 3.70-4.12 (3H, m, H-4', 5', 5''), 4.57 (1H, m  
H-3'), 6.41 (1H, dd, H-1', J<sub>1',2'</sub> = 7.93, J<sub>1',2''</sub> = 6.10  
Hz), 7.26-7.76 (11H, m, H-6 and Ph), 8.94 (1H, s, NH,  
exchangeable).

20 Microanalysis (C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>Si). Calcd: C, 64.97; H, 6.71;  
N, 5.83. Found: C, 65.05; H, 6.75; N, 5.91.

By following the same procedure but using the corresponding 2'-substituted nucleoside analogs as starting materials,  
25 the following compounds are also prepared:

1-(5'-0-tert-Butylldiphenylsilyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine.

1-(5'-0-tert-Butylldiphenylsilyl-2-chloro-2-deoxy-β-D-arabinofuranosyl)thymine.  
30

1-(5'-0-tert-Butylldiphenylsilyl-2-bromo-2-deoxy-β-D-arabinofuranosyl)thymine.

1-(5'-0-tert-Butylldiphenylsilyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)thymine.

15 1-(5'-0-tert-Butylldiphenylsilyl-2-chloro-2-deoxy-β-D-ribofuranosyl)thymine.

1 1-(5'-O-tert-Butyldiphenylsilyl-2-bromo-2-deoxy-β-D-  
ribofuranosyl)thymine.

5 EXAMPLE 3.

To a solution of 5-methyluridine (3.00 g, 10.06 mmol)  
and tert-butyldiphenylsilyl chloride (6.50 ml, 25.0  
mmol) in dry N,N-dimethylformamide (60 ml) is added  
10 imidazole (3.00 g, 44.07 mmol), and the mixture is  
stirred overnight at room temperature. The solvent is  
removed in vacuo and the residue is partitioned between  
methylene chloride and water. The organic layer is sepa-  
rated, washed twice with water and concentrated in  
15 vacuo. The residue is chromatographed over a column of  
silica gel G60 using carbon tetrachloride-acetone (10:1)  
as the eluent. Two fractions are obtained. Upon evapora-  
tion of the first fraction in vacuo and crystallization  
of the residue from carbon tetrachloride-petroleum  
20 ether, 1-(2',5'-di-O-tert-butyldiphenyl-β-D-ribofura-  
nosyl)thymine (3.78 g, 51 %) is obtained, mp 97-99°C.  
1H NMR (CDCl<sub>3</sub>) 0.92 (9H, s, t-Bu), 1.11 (9H, s, t-  
Bu), 1.58 (3H, d, 5-Me, J<sub>Me,6</sub> = 1.24 Hz), 3.73 (1H, dd,  
H-5', J<sub>5',5''</sub> = 11.73, J<sub>4',5''</sub> = 1.64), 3.91 (1H, dd, H-  
25 5'', J<sub>5',5''</sub> = 11.73, J<sub>4',5''</sub> = 1.92), 4.18 (1H, m, H-  
4'), 4.39 (2H, m, H-2',3'), 6.20 (1H, m, H-1'), 6.78  
(1H, d, H-6, J<sub>Me,6</sub> = 1.24), 7.10-7.71 (20H, m, Ph), 7.81  
(1H, broad s, NH, exchangeable).

30 Microanalysis (C<sub>42</sub>H<sub>50</sub>N<sub>2</sub>O<sub>6</sub>Si<sub>2</sub>·2H<sub>2</sub>O) Calcd: C, 65.21; H,  
7.06; N, 3.63. Found: C, 65.20; H, 7.10; N, 3.44.

From the second fraction, 1-(3',5'-di-O-tert-butyldi-  
phenylsilyl-β-D-ribofuranosyl)thymine (1.86 g, 25 %) is  
35 obtained, after crystallization from benzene-hexane, mp  
86-89°C. 1H NMR (CDCl<sub>3</sub>) 0.96 (9H, s, t-Bu), 1.13 (9H,  
s, t-Bu), 1.49 (3H, s, 5-Me), 2.81 (1H, dd, H-5',

- 1  $J_{5',5''} = 11.66$ ,  $J_{4',5'} = 1.92$ , 3.54 (1H, dd, H-5'',  
 $J_{5',5''} = 11.66$ ,  $J_{4',5''} = 1.88$ ). 3.77 (1H, m, H-4'),  
4.19 (1H, m, H-3'), 4.46 (1H, m, H-2'), 6.16 (1H, d, H-  
1',  $J_{1',2'} = 7.68$ ), 7.08-7.78 (21H, m, H-6 and Ph), 8.35  
5 (1H, s, NH, exchangeable).

Microanalysis (C<sub>42</sub>H<sub>50</sub>N<sub>2</sub>O<sub>6</sub>Si<sub>2</sub>) Calcd: C, 68.63; H, 6.80;  
N, 3.81. Found: C, 68.74; H, 7.09; N, 3.65.

- 10 By following the same procedure but using 1-( $\beta$ -D-  
arabinofuranosyl)thymine as the starting material, 1-  
(3',5'-di-O-tert-butyldiphenylsilyl- $\beta$ -D-arabinofurano-  
syl)thymine and 1-(2,5-di-O-tert-butyldiphenylsilyl- $\beta$ -D-  
arabinofuranosyl)thymine are also prepared.

15

## EXAMPLE 4

- A mixture of 3',5'-di-O-acetylthymidine (4.50 g, 13.78  
20 mmol) in carbon tetrachloride (900 ml) is refluxed under  
nitrogen until a clear solution is obtained. A solution  
of bromine (0.8 ml, 15.61 mmol) in carbon tetrachloride  
(18 ml) is very slowly added to the refluxing solution  
over a period of 2 to 3 hours, while the reaction mix-  
25 ture is irradiated with a 500 watt UV lamp. After all  
the bromine is added, nitrogen is bubbled through the  
solution for 30 minutes to remove hydrogen bromide. The  
solution is concentrated to dryness in vacuo. The crude  
5-bromomethyl-uracil nucleoside intermediate thus ob-  
30 tained is dissolved in anhydrous acetonitrile (50 ml)  
and treated with powdered silver fluoride (8 g, 63.10  
mmol) for 15 minutes with vigorous stirring at room  
temperature. The precipitate is removed by filtration  
and the filtrate is concentrated to dryness in vacuo.  
35 The residue is dissolved in chloroform, washed successi-  
vely with water and saline, dried over sodium sulfate  
and concentrated to dryness. The residue is chromatogra-

1 phed on a column of silica gel G60 using n-hexane-ethyl  
 ac tat (1:1). Upon evaporation of the major fraction in  
 vacuo and crystallization of the residue from methylene  
 chloride-ether-petroleum ether, 1-(3',5'-di-O-acetyl- $\beta$ -  
 5 D-erythropentofuranosyl)-5-monofluoromethyluracil (1.5  
 g, 32.%) is obtained, mp 24-27° C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.12  
 (6H, s, 3',5'-Ac), 2.24 (1H, m, H-2'), 2.57 (1H, dq, H-  
 2'',  $J_{2',2''} = 14.27$ ,  $J_{1',2''} = 5.77$ ,  $J_{2'',3} = 2.06$ ),  
 4.31 (3H, m, H-4',5',5''), 5.19 (2H, dd, CH F,  $J_{2',3} =$   
 10 47.48,  $J_{\text{H,H}} = 3.29$ ), 5.25 (1H, m, H-3'), 6.32 (1H, dd,  
 H-1',  $J_{\text{H,H}} = 8.24$ ,  $J_{1',2''} = 5.77$ ), 7.69 (1H, d, H-6,  
 $J_{6,\text{F}} = 2.47$ ).

Microanalysis ( $\text{C}_{14}\text{H}_{17}\text{FN}_2\text{O}_7$ ) Calcd: C, 48.84; H, 4.98;  
 15 F, 5.52; N, 8.14. Found: C, 49.14; H, 5.21; F, 5.21; N,  
 7.87.

#### EXAMPLE 5

20

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro- $\beta$ -D-arabinofura-  
 nosyl)thymine (170 mg, 0.49 mmol) is brominated by a  
 procedure described in Example 4. The crude 5-bromo-  
 methyluracilnucleoside is dissolved in anhydrous tetra-  
 25 hydrofuran (1 ml) and 0.5 M tetra-n-butylammonium  
 fluoride in tetrahydrofuran (2 ml) is added. The mixture  
 is stirred for 30 minutes at room temperature and then  
 chromatographed on a silica gel G60 column using n-  
 hexane-ethyl acetate (1:2) as the eluent. 1-(3,5-Di-O-  
 30 acetyl-2-deoxy-2-fluoro- $\beta$ -D-arabinofuranosyl)-5-Mono-  
 fluoromethyluracil (22 mg, 12 %) is obtained after con-  
 centration of the nucleoside-containing fraction and  
 crystallization of the residue from benzene; mp 109-110°  
 C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.12 (3H, s, Ac), 2.17 (3H, s, Ac),  
 35 4.26 (1H, m, H-4'), 4.46 (2H, m, H-5',5''), 5.13 (1H,  
 dd, H-2',  $J_{2',3} = 50.22$ ,  $J_{1',2'} = 2.74$  Hz), 5.18 (2H, d,  
 CH F,  $J_{2',\text{F}} = 47.74$ ), 5.24 (1H, dd, H-3',  $J_{3',\text{F}} = 16.60$ ,  
 $J_{2',\text{H}} = 2.47$ ).

1  $J_{2',3'} = 2.06$ ), 6.22 (1H, dd, H-1',  $J_{1',F} = 21.40$ ,  
 $J_{1',2'} = 2.74$ ), 7.73 (1H, broad s, H-6), 9.36 (1H, broad  
 s, NH, exchangeable).

5 Microanalysis ( $C_{14}H_{16}F_2N_2O_7$ ) Calcd: C, 46.41; H, 4.45;  
 F, 10.49; N, 7.73. Found: C, 46.15; H, 4.51; F, 10.31;  
 N, 7.75.

# 10 EXAMPLE 6

Crude 1-(5'-O-tert-butyldiphenylsilyl-2'-deoxy- $\beta$ -D-  
 erythropentofuranosyl)-5-monobromouracil (obtained by  
 bromination of 5-O-tert-butyldiphenylsilylthymidine (120  
 15 mg, 0.25 mmol) is dissolved in dry acetone (5 ml) and  
 amberlyst A-26 (F<sup>-</sup>) (0.5 g) is added. The mixture is  
 vigorously stirred at room temperature for 1 hour and  
 the resin is filtered and washed with acetone. The  
 concentrated filtrate and washings are concentrated in  
 20 vacuo and the residue chromatographed over a column of  
 silica gel G60 using n-hexane-ethyl acetate (1:3). 1-  
 (5'-O-tert-Butyldiphenylsilyl-2'-deoxy- $\beta$ -D-erythropento-  
 furanosyl)-5-monofluorouracil (26 mg, 21 %) is obtained  
 in pure form after crystallization from n-hexane-  
 25 methylene chloride, mp 129-131°C.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.04  
 (3H, s, Me in tBu), 1.08 (6H, s, 2Me in tBu), 1.96-2.62  
 (2H, m, H-2',2''), 3.75-4.19 (3H, m, H-4',5',5''), 4.80  
 (2H, d, CH<sub>2</sub>F,  $J_{H,F} = 47.92$  Hz), 6.22 (1H, dd, H-1',  
 $J_{1',2'} = 5.76$ ,  $J_{1',F} = 7.41$ ), 7.29-7.77 (10H, m, Ph),  
 30 7.83 (1H, d, H-6,  $J_{6,F} = 3.35$ ), 8.45 (1H, broad s, NH,  
 exchangeable).

Microanalysis ( $C_{26}H_{21}FN_2O_5Si$ ) Calcd: C, 62.63; H, 6.27;  
 F, 3.81; N, 5.62. Found: C, 62.66; H, 6.36; F, 3.66; N,  
 35 5.78.

- 1 The following 5-monofluoromethyluracil nucleosides are prepared by following the same procedures described in Example 4 and Example 6 but using the corresponding blocked nucleoside intermediates. When the silver fluoride-acetone combination as in Example 4 is used, the yields are 30 % - 55 %, whereas the Amberlyst A-26 (F<sup>-</sup>)-acetone procedure as in Example 6 gives the following products in 20 % - 40 % yields:
- 10 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-monofluoromethyluracil  
1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil  
1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 15 1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-monofluoromethyluracil.  
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil.
- 20 1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil.  
1-(2',3',5'-Tri-O-acetyl-β-D-arabinofuranosyl)-5-monofluoromethyluracil  
1-(2',5'-Di-O-tert-butyl-diphenylsilyl-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 25 1-(3',5'-Di-O-tert-butyl-diphenylsilyl-β-D-arabinofuranosyl)-monofluoromethyluracil  
3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine
- 30 3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-monofluoromethyluridine  
3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine  
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine.
- 35 5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-monofluoromethyluridine.



- 1 5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine.  
2',3',5'-Tri-0-acetyl-5-monofluoromethyluridine  
2',5'-Di-0-tert-butylidiphenylsilyl-5-  
5 monofluoromethyluridine  
3',5'-Di-0-tert-butylidiphenylsilyl-5-monofluoromethyluridine

By following the procedure of Example 5 but using the  
10 corresponding acetylated nucleosides as the intermediates, the following nucleosides are also prepared in 10 % - 20 % yield.

- 1-(3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil  
15 1-(3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil  
1-(2',3',5'-Tri-0-acetyl-β-D-arabinofuranosyl)-5-monofluoromethyluracil  
20 3',5'-Di-0-acetyl-2'-deoxy-5-monofluoromethyluridine  
3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine  
3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-5-monofluoromethyluridine  
25 3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine  
2',3',5'-Tri-0-acetyl-5-monofluoromethyluridine.

30 EXAMPLE 7

A solution of bromine (0.118 ml, 2.30 mmol) in carbon tetrachloride (2 ml) is slowly blown with a stream of dry nitrogen into a refluxing solution of 1-(5'-0-tert-butylidiphenylsilyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)thymine (498 mg, 1 mmol) in carbon tetrachloride  
35 while irradiated with a UV light. After 30 minutes, when

- 1 all the bromine is added, nitrogen is bubbled through the solution for a further 15 minutes to remove the hydrogen bromide.
- 5 The solution is concentrated to dryness in vacuo and the residue dissolved in dry acetonitrile (100 ml). Finely pulverized silver fluoride (1.0 g, 7.88 mmol) is added to the solution and the mixture is stirred vigorously for 15 minutes at room temperature. The mixture is
- 10 filtered and the filtrate is concentrated in vacuo. The residue is dissolved in chloroform, washed with water and saline, dried over sodium sulfate and concentrated in vacuo. The residue is chromatographed on a column of silica gel G60 using methylene chloride - tetrahydro-
- 15 furan (20:1 to 10:1) as the eluent. The UV absorbing fraction eluted with 10:1 methylene chloride - tetrahydrofuran is concentrated and the residue crystallized from methylene chloride - petroleum ether. 1-(5'-O-tert-Butyldiphenylsilyl)-2'-deoxy-2'-fluoro- $\beta$ -D-arabinofurano-
- 20 syl)-5-difluoromethyluracil (80 mg, 15 %) is obtained, mp 132-134 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.08 (9H, s, tBu), 3.75-4.09 (3H, m, H-4',5',5''), 4.55 (1H, dq, H-3', J<sub>2',3'</sub> = 22.23, J<sub>2',3'</sub> = 0.82, J<sub>3',4'</sub> = 0 Hz), 5.05 (1H, dq, H-2', J<sub>2',3'</sub> = 51.05, J<sub>1',2'</sub> = 3.30, J<sub>2',3'</sub> = 0.82), 6.77
- 25 (1H, dd, H-1', J<sub>1',2'</sub> = 19.49, J<sub>1',2'</sub> = 3.30) 6.56 (1H, t, CHF<sub>2</sub>, J<sub>H,F</sub> = 54.75). 7.23-7.81 (10H, m, Ph), 7.87 (1H, d, H-6, J<sub>6,F</sub> = 1.37), 8.79 (1H, broad s, NH, exchangeable).

Microanalysis (C<sub>26</sub>H<sub>29</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>Si) Calcd: C, 58.41; H, 5.47; F, 10.66; N, 5.24. Found: C, 58.58; H, 5.69; F, 10.49; N, 5.19.

By following the same procedure but using the corresponding protected nucleosides, the following 5-difluoromethyluracil nucleosides are prepared:

- 1 1-(3',5'-Di-O-acetyl-2'-deoxy-β-D-erythropentofuranosyl)-5-difluoromethyluracil  
1-(2',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 5 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil  
1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil  
1-(2',3',5'-Tri-O-acetyl-β-D-arabinofuranosyl)-5-
- 10 difluoromethyluracil  
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil  
1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 15 1-(2',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-5-difluoromethyluracil  
1-(3',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-5-difluoromethyluracil  
3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-
- 20 difluoromethyluridine  
3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-difluoromethyluridine  
3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-difluoromethyluridine
- 25 2',3',5'-Tri-O-acetyl-5-difluoromethyluridine  
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine  
5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-difluoromethyluridine
- 30 5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-difluoromethyluridine  
2',5'-Di-O-tert-butyldiphenylsilyl-5-difluoromethyluridine  
3',5'-Di-O-tert-butyldiphenylsilyl-5-
- 35 difluoromethyluridine.

## 1 EXAMPLE 8

1-(5'-O-t rt-Butyldiphenylsilyl-2'-deoxy- $\beta$ -D-erythro-pentofuranosyl)-5-monofluoromethyluracil (440 ml, 0.88 mmol) is dissolved in dry tetrahydrofuran (4 ml) and 0.5 M tetra-n-butylammonium fluoride in tetrahydrofuran (2.2 ml) is added. The mixture is stirred at room temperature for 90 minutes and then concentrated in vacuo. The residue is chromatographed on a silica gel G60 column using methylene chloride-tetrahydrofuran (1:1) as the eluent. After concentration of the UV absorbing fraction, the residue is crystallized from acetone to give 2'-deoxy-5-monofluoromethyluridine, 143 mg (63 %), mp 140° C (dec). <sup>1</sup>H MNR (d<sub>6</sub>-acetone)  $\delta$  2.21 (2H, m, H-2', 2''), 3.71 (2H, m, H-5', 5''), 3.88 (1H, apparent dd, H-4', J<sub>3,4'</sub> = 3.16, J<sub>4',5'</sub> = 6.17, J<sub>4',5''</sub> = 0 Hz), 4.39 (1H, m, H-3'), 4.96 (2H, d, CH<sub>2</sub>F, J<sub>H,F</sub> = 49.12), 6.20 (1H, apparent t, H-1', J<sub>1',2'</sub> = J<sub>1',2''</sub> = 6.59, 8.23 (1H, d H-6, J<sub>6,F</sub> = 4.12).

Microanalysis (C<sub>10</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>5</sub>) Calcd: C, 46.16; H, 5.03; F, 7.30; N, 10.76. Found: C, 46.28; H, 5.31; F, 7.16; N, 10.58.

By following the same procedure but using the corresponding silylated nucleoside intermediates, the following 5-(partially fluorinated) methyluracil nucleosides are prepared:

- 1-(2'-Deoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluracil
- 1-(2'-Chloro-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluracil
- 1-(2'-Bromo-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluracil
- 1-( $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluracil

- 1 2'-Deoxy-2'-fluoro-5-monofluoromethyluridine  
2'-Chloro-2'-deoxy-5-monofluoromethyluridine  
2'-Bromo-2'-deoxy-5-monofluoromethyluridine  
5-Monofluoromethyluridine
- 5 1-(2'-Deoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl)-5-  
difluoromethyluracil  
1-(2'-Chloro-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-  
difluoromethyluracil  
1-(2'-Bromo-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-  
10 difluoromethyluracil  
1-( $\beta$ -D-Arabinofuranosyl)-5-difluorouracil  
2'-Deoxy-5-difluoromethyluridine  
5-Difluoromethyluridine  
2'-Deoxy-2'-fluoro-5-difluoromethyluridine
- 15 2'-Chloro-2'-deoxy-5-difluoromethyluridine  
2'-Bromo-2'-deoxy-5-difluoromethyluridine.

The results of antiviral assay of some representative nucleosides are given in Table I.

20

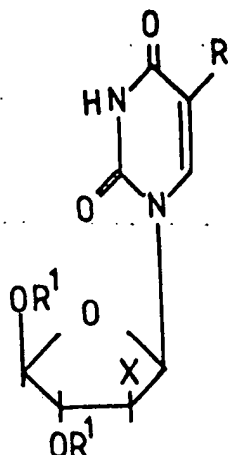
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1 TABLE I.

Antitherpes Activity of  $\alpha$ -fluorinated thymine nucleosides



Inhibitory Concentration ( $\mu$ M)      Toxic Concentration ( $\mu$ M)

R	R1	X	HSV-1	HSV-2	
CH <sub>2</sub> F	H	H	>100	>100	1,000
CH <sub>2</sub> F	Ac	H	>100	>100	1,000
CHF <sub>2</sub>	H	H	1.40	1.66	1,000
CHF <sub>2</sub>	Ac	H	17.0	25.1	1,000
CH <sub>2</sub> F	H	F	0.21	0.18	1,000
CH <sub>2</sub> F	Ac	F	2.46	5.19	1,000
CHF <sub>2</sub>	H	F	0.48	1.04	1,000
CHF <sub>2</sub>	Ac	F	0.71	2.16	1,000
(FMAU) CH <sub>3</sub>	H	F	0.10	0.05	1,000
CH <sub>3</sub>	Ac	F	0.44	1.23	1,000

	Inhibitory Concentration ( $\mu$ M)			Toxic Concentration ( $\mu$ M)		
	R	R1	X	HSV-1	HSV-2	
20	CH <sub>2</sub> F	H	H	>100	>100	1,000
	CH <sub>2</sub> F	Ac	H	>100	>100	1,000
	CHF <sub>2</sub>	H	H	1.40	1.66	1,000
	CHF <sub>2</sub>	Ac	H	17.0	25.1	1,000
	CH <sub>2</sub> F	H	F	0.21	0.18	1,000
	CH <sub>2</sub> F	Ac	F	2.46	5.19	1,000
25	CHF <sub>2</sub>	H	F	0.48	1.04	1,000
	CHF <sub>2</sub>	Ac	F	0.71	2.16	1,000
	(FMAU) CH <sub>3</sub>	H	F	0.10	0.05	1,000
	CH <sub>3</sub>	Ac	F	0.44	1.23	1,000

30

35

- 1 Each of the nucleosides was initially dissolved in a  
diluent containing 60 % propylene glycol and 10 % EtOH;  
subsequent dilutions used maintenance culture medium.  
Agents were assessed at tenfold dilutions with final  
5 concentrations ranging from 10,000 to 0.01 micromolar.

Confluent human foreskin monolayers were maintained in  
96-well microtiter plates using Eagle's Minimal Essen-  
tial Medium supplemented with 2 % fetal bovine serum,  
10 antibiotics and glutamine using standard methods.  
Prior to virus inoculation, the medium was removed from  
each well and replaced with 100  $\mu$ l of agent diluted in  
maintenance medium with differing concentrations in each  
horizontal row, beginning with the highest concentration  
15 in the upper row, with subsequent tenfold dilutions in  
the next rows and the last (control) row fed with agent-  
free maintenance medium. The virus inocula were then  
added, suspended in 100  $\mu$ l of maintenance medium. A  
high-dose inoculum which induced nearly confluent (100  
20 %) cytopathic effect (CPE) two days later was added to  
the first five vertical columns of the plate (1-5) and,  
similarly, a low-dose inoculum inducing approximately 50  
% CPE in each well two days later was added to the next  
five vertical columns (6-10). To the last two columns,  
25 virus-free medium was added to serve as uninfected con-  
trol wells in order to assess direct cellular cytotoxi-  
city at each agent dilution. The plates were then incu-  
bated at 36.9<sup>0</sup> C in 9 % CO<sub>2</sub> in air for two days, at  
which time they were read.

30

The cytopathology of each well was read using an inver-  
ted microscope and scored from 0 to 4 (0 = no CPE and 4  
= > 95 % CPE); for marginal or equivocal readings a + or  
- is affixed to each score. For calculation of the  
35 inhibitory concentrations (IC) of agents and interpola-  
ting between dilutions of agents, each well reading was  
converted to a numerical score (4 = 40, 4- = 37, 3+ = 33,

1 3 = 30, tc). The mean score of each five wells in a row  
Receiving a given agent dilution and virus inoculum was  
then calculated and compared with an appropriate control  
row receiving no agent. Significant inhibition was judged  
5 to occur when the mean well score at a given agent  
concentration was lower than the mean value of the  
control row by 10 scoring units. When the value fell  
between two rows, simple arithmetic interpolation was  
done to calculate the agent concentration at the point on  
10 a slope between the mean scores in the rows above and  
below this point. The IC values of each agent using the  
high and low virus inocula were then averaged yielding a  
final mean IC which was expressed as a micromolar drug  
concentration.

15 Although  $\alpha,\alpha,\alpha$ -trifluorothymidine (Formula IV,  $R = CF_3$ ,  
 $X = H$ ,  $R^1 = H$ ) is reported to be antiherpetic and very  
cytotoxic, the  $\alpha,\alpha$ -difluoro analog (Formula IV,  $R =$   
 $CHF_2$ ,  $X = H$  or  $Ac$ ,  $R^1 = H$ ) showed very potent antiherpes  
20 activity without serious cytotoxicity. In the FMAU series,  
fluorination of the 5-methyl group does not alter  
the antiherpetic activity significantly.

The acetylated derivatives may act as masked precursors  
26 which may be saponified by esterases to release active  
free nucleosides. The  $^{18}F$ -labeled nucleosides which can  
be prepared by the method we developed may be useful for  
diagnosis of herpes encephalitis, employing Positron  
Emission Tomography scanning.

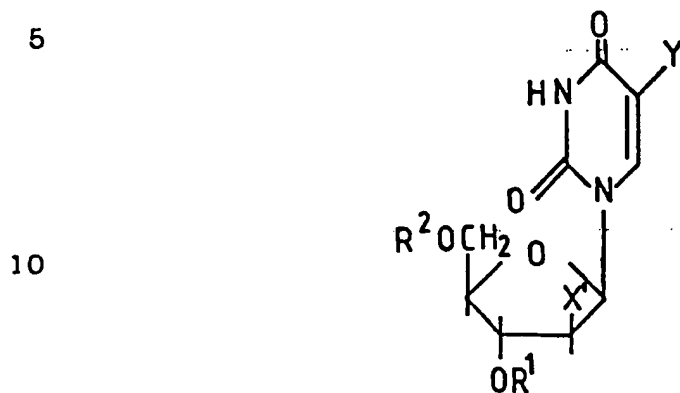
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## 1 CLAIMS :

1. Pyrimidine nucleosides having the formula



wherein:

X or X' is H

15 X or X' is a halogen, pseudohalogen or OR³ wherein  
R³ is H, acyl or trisubstituted-silyl;

Y is CH<sub>1</sub>F or CHF<sub>2</sub>;

R¹ and R² are the same or different and are H, acyl or trisubstituted-silyl.

20

2. Nucleosides of Claim 1 selected from the group of:

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)thymine

1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)thymine

1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)thymine

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo-β-D-arabinofuranosyl)thymine

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-ribofuranosyl)thymine

1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-ribofuranosyl)thymine

1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-ribofuranosyl)thymine

35

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo-β-D-ribofuranosyl)thymine.

- 1 3. Nucleosides of Claim 1 selected from the group of:  
5'-O-tert-Butyldiphenylsilylthymidine  
1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-  
β-D-arabinofuranosyl)thymine  
5 1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-  
β-D-arabinofuranosyl)thymine  
1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-  
β-D-arabinofuranosyl)thymine  
1-(2',5'-Di-O-tert-butyl-diphenylsilyl-β-D-arabino-  
10 furanosyl)thymine  
1-(3',5'-Di-O-tert-butyl-diphenylsilyl-β-D-arabino-  
furanosyl)thymine  
1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-  
β-D-ribofuranosyl)thymine  
15 1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-  
β-D-ribofuranosyl)thymine  
1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-  
β-D-ribofuranosyl)thymine  
1-(2',5'-Di-O-tert-butyl-diphenylsilyl-β-D-ribofura-  
20 nosyl)thymine  
1-(3',5'-Di-O-tert-butyl-diphenylsilyl-β-D-ribofura-  
nosyl)thymine.
4. Nucleosides of Claim 1 selected from the group of:  
26 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-  
arabinofuranosyl)-5-monofluoromethyluracil  
1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-  
arabinofuranosyl)-5-monofluoromethyluracil  
1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-  
30 arabinofuranosyl)-5-monofluoromethyluracil  
1-(2',3',5'-Tri-O-acetyl-β-D-arabinofuranosyl)-5-  
monofluoromethyluracil  
3',5'-Di-O-acetyl-2'-deoxy-5-monofluoromethyluridine  
3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-  
35 monofluoromethyluridine  
3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-  
monofluoromethyluridine

- 1 3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine  
2',3',5'-Tri-O-acetyl-5-monofluoromethyluridine.
- 5 5. Nucleosides of Claim 1 selcted from the group of:  
1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-  
β-D-arabinofuranosyl)-5-monofluoromethyluracil  
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-  
β-D-arabinofuranosyl)-5-monofluoromethyluracil  
10 1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-  
β-D-arabinofuranosyl)-5-monofluoromethyluracil  
1-(2',5'-Di-O-tert-butylldiphenylsilyl-β-D-  
arabinofuranosyl)-5-monofluoromethyluracil  
1-(3',5'-Di-O-tert-butylldiphenylsilyl-β-D-  
15 arabinofuranosyl)-5-monofluoromethyluracil  
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-5-  
monofluormethyluridine  
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-  
monofluoromethyluridine  
20 5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-  
monofluoromethyluridine  
5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-  
monofluoromethyluridine  
2',5'-Di-O-tert-butylldiphenylsilyl-5-  
25 monofluoromethyluridine  
3',5'-Di-O-tert-butylldiphenylsilyl-5-  
monofluoromethyluridine.
6. Nucleosides of Claim 1 selceted from the group of:  
30 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-  
arabinofuranosyl)-5-difluoromethyluracil  
1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-  
arabinofuranosyl)-5-difluoromethyluracil  
1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-  
35 arabinofuranosyl)-5-difluoromethyluracil  
3',5'-Di-O-acetyl-2'-deoxy-5-difluoromethyluridine

- 1 3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine  
3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-difluoromethyluridine  
5 3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-difluoromethyluridine  
2',3',5'-Tri-O-acetyl-5-difluoromethyluridine.
7. Nucleosides of Claim 1 selected from the group of:  
10 1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
15 1-(2',5'-Di-O-tert-butyl-diphenylsilyl- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
1-(3',5'-Di-O-tert-butyl-diphenylsilyl- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
20 5'-O-tert-Butyldiphenylsilyl-2'-deoxy-5-difluoromethyluridine  
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine  
5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-difluoromethyluridine  
25 5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-difluoromethyluridine  
2',5'-Di-O-tert-butyl-diphenylsilyl-5-difluoromethyluridine  
30 3',5'-Di-O-tert-butyl-diphenylsilyl-5-difluoromethyluridine.
8. Nucleosides of Claim 1 selected from the group of:  
35 1-(2'-Deoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluracil  
1-(2'-Chloro-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluracil

- 1 1-(2'-Bromo-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluracil  
1-( $\beta$ -D-arabinofuranosyl)-5-monofluoromethyluridine  
5-Monofluoromethyluridine
- 5 2'-Deoxy-5-monofluoromethyluridine  
2'-Deoxy-2'-fluoro-5-monofluoromethyluridine  
2'-Deoxy-2'-chloro-5-monofluoromethyluridine  
2'-Deoxy-2'-bromo-5-monofluoromethyluridine.
- 10 9. Nucleosides of Claim 1 selected from the group of:  
1-(2'-Deoxy-2'-fluoro- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
1-(2'-Chloro-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil
- 15 1-(2'-Bromo-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
1-( $\beta$ -D-arabinofuranosyl)-5-difluoromethyluracil  
5-Difluoromethyluridine  
2'-Deoxy-5-difluoromethyluridine
- 20 2'-Deoxy-2'-fluoro-5-difluoromethyluridine  
2'-Chloro-2'-deoxy-5-difluoromethyluridine  
2'-Bromo-2'-deoxy-5-difluoromethyluridine.
10. Pharmaceutical composition comprising an effective  
25 amount of nucleoside of formula defined in Claim 1.

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